Farah Saeed

in support of WORLD CANCER RESEARCH DAY

September 24th

2024 Campaign

INNOVATION IN CANCER RESEARCH DRIVES PROGRESS TOWARDS HEALTH EQUITY

p53 signalling and cancer

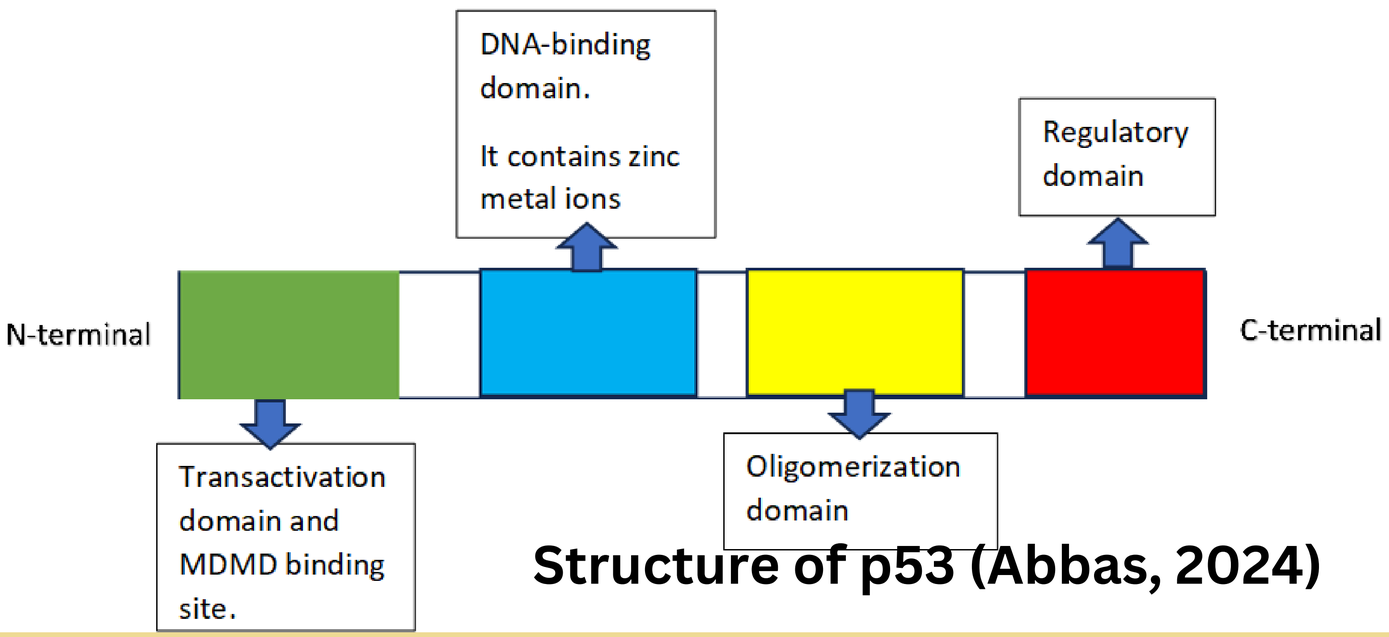
By Dr Hafsa Waseela Abbas

It is encoded by the TP53 gene to form the protein with a molecular mass of 53 kDa (Pecorino, 2012).

It was the first tumour suppressor gene identified.

It is also known as the guardian of the genome because it regulates gene expression, and coordinates DNA repair of damaged cells which prevents the rise of further mutations (Pecorino, 2012; Jaber 2024).

There are two other members within p53 family: p63 and p73. Some functions are similar e.g. apoptosis (cell death) where they can connect with most p53-responsive promoters and initiate transcription but have separate roles in maintaining homeostasis and development (Pecorino, 2012).



Structure of p53 (Abbas, 2024)

GLOSSARY

Gene: Hereditary unit and short section of DNA that helps determine characteristics of an organism.

Genome: Complete genetic composition of a cell.

Homeostasis: The maintenance of the internal environment of the body by adjusting to optimal conditions for survival e.g. water and ion concentration, glucose levels and temperature.

Transcription: The process of using DNA as a template to make the single strand of nucleotide called ribonucleic acid (RNA).

Transcription factor: A protein that helps transcribing genes by affecting the enzyme RNA polymerase.

Translation: The process of using an mRNA molecule, type of mRNA, as a template to make a protein.

Tumour suppressor: A gene that encodes a protein to stop cancer growth

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Dual role:

1) **Transcription factor:** Regulates cell division, tumour microenvironment, cell death, immune system, cell cycle, cell differentiation, metabolism and maintain genomic integrity.

For example: it upregulates genes that encode enzymes such as glutathione peroxidase 1 and sestrins – This increases antioxidant activity against mutations and prevent cancer.

2) **Initiate apoptosis**: Inducing DNA damage, cell cycle arrest and inhibit angiogenesis. This is caused by stress by oxidative, radiation, drugs and carcinogens.

It interacts of p53 with apoptosis-stimulating proteins of p53 (ASPP) proteins, as well as p300.

(Mirzayans *et al.* 2012; Sui *et al.* 2011; Liebl and Hofmann, 2021; Marei *et al.* 2021)

GLOSSARY

- **Carcinogen: Cancer-causing agent**
- **Cell cycle: The phases in how cells divides and grow**
- **Differentiation: Changes to cell shape and function when unspecialised cells become specialised for specific functions.**
- **Gene: Hereditary unit and short section of DNA that helps determine characteristics of an organism.**
- **Genome: Complete genetic composition of a cell.**
- **Metabolism: A series of chemical and physical reaction changes to support life.**
- **Mutation: A random change in the DNA that affects that particular gene or chromosome.**
- **Radiation: The transfer of energy as waves or particles through space or a material.**
- **Radiotherapy: The treatment of cancer using radiation e.g. x-rays.**
- **Transcription factor: A protein that helps transcribing genes by affecting the enzyme RNA polymerase.**
- **Translation: The process of using an mRNA molecule, type of mRNA, as a template to make a protein.**
- **Tumour microenvironment: It is made of cells that are non-malignant (does not spread or non-harmful) that interact with one another or with cancer cells. This can influence cancer progression and treatment response.**

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WHEN P53 IS MUTATED

p53 can lose its function by two mechanisms:

Mutation of p53 gene - **STOP TUMOUR SUPPRESSOR ROLE.**

Overexpression of MDM2 or MDMX - Both proteins commonly negatively regulate p53 levels (decrease its levels), overexpression can **PREVENT P53 ACTIVITY AND CREATE AN ONCOGENIC ROLE** (Peuget, Zhou and Selivanova, 2024)

What are the most common types of mutations?

- 90% of p53 mutations have missense mutations found in the DNA-binding domain.
- Over 75% of p53 mutations lead onto amino acid substitution.

What effect this will have?

- Damaged cells continue to replicate DNA to increase damage and evade apoptosis, survival and cancer growth.
- This is achieved inactivating p53/p21/Cip1 complex with and without the Ras protein stimulation.

(Mirzayans *et al*. 2012; Sui *et al.* 2011; Liebl and Hofmann, 2021; Marei *et al*. 2021)

50% of human cancers caused by mutations:
breast. lung, pancreas, liver, prostate, bladder, skin and colon.
(Mirzayans *et al*. 2012; Sui *et al*. 2011; Liebl and Hofmann, 2021; Marei *et al*. 2021)

GLOSSARY

Tumour suppressor: A gene that encodes a protein to stop cancer growth.

Mutation: A random change in the DNA that affects that particular gene or chromosome.

Oncogene: A mutated form of a gene that leads to uncontrolled growth of cancer cells.

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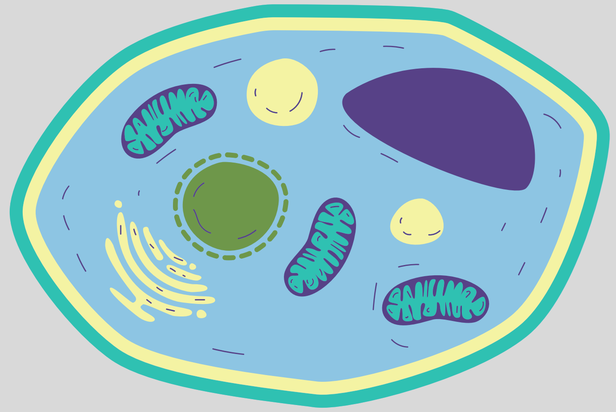
POSITIVE REGULATION OF P53

p21 regulates p53 and its kinase enzyme, ataxia telangiectasia mutated (ATM) – This helps control **gene expression**, **prevent apoptosis (cell death)** and **inhibit cell cycle** between G1 and S phase.

G1 phase - growth phase

S- replication phase

p21 binds to the **proliferating cell nuclear antigen (PCNA)** that functions in **DNA synthesis and repair**. This prevents **DNA replication but has no effect on DNA repair.**



DNA - genetic material

DNA synthesis - The production of DNA

DNA replication - The production of two identical copies from the original DNA template.

(Mirzayans *et al.* 2012; Sui *et al*. 2011; Liebl and Hofmann, 2021; Marei *et al.* 2021)

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NEGATIVE REGULATION OF P53

p53 stimulates MDM2 for transcription, however, **MDM2 negatively regulates p53 and causes its degradation.**

M**DM2 is a ubiquitin ligase enzyme that binds** to **a small peptide called ubiquitin.**

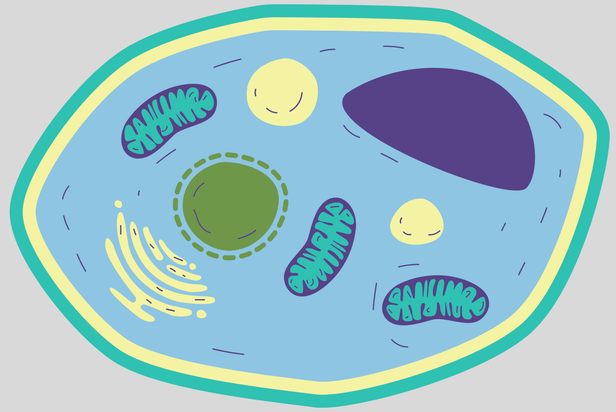
Ubiquitin then binds to p**roteins that are labelled for proteolysis** where it **cleaves peptide bonds and inhibits p53 transcriptional domain** in the N terminal to i**ncrease proto-oncogene activity.**

This leads to a **change in the C-terminal of p53 protein**.

The p**53 protein leaves the nucleus** and is tr**ansported to the cytoplasm targeted for proteosome.**

They commonly have l**ow levels of p53, the activity depends on protein degradation.**

It help **decrease MDMD synthesis and increase activity.**



(Mirzayans *et al.* 2012; Sui *et al*. 2011; Liebl and Hofmann, 2021; Marei *et al.* 2021)

Farah With Me Cancer Project is part of Farah Saeed Trust, a voluntary organisation that aims to inspire, educate and help others. Farah With Me aims to raise public awareness on cancer through virtual and in-person event. World Cancer Research Day is not affliiated with FST, however, FST enjoys partaking in its annual research initiatives.

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p53 interacts with histone/lysine acetyltransferase (HATS) to evade MDM2

PATHWAY ONE

1. **DNA damage caused by ionizing radiation**
2. **This is signalled by two protein kinases:**
   - **The first kinase, ATM (ataxia telangiectasia mutated), stimulated by DNA double-strand breaks, phosphorylates p53 at the amino acid residue serine 15.**
   - **ATM kinase activates a second kinase checkpoint kinase 1 Chk2.**
3. **Both ATM and Chk2 kinases phosphorylate amino-terminal sites of p53.**

This phosphorylation interferes with binding of MDM2.

PATHWAY TWO

1. **Stress signal by two different kinases: ataxia-telangiectasia-mutated-and-Rad3-related kinase (ATR) and casein kinase II.**
2. **They phosphorylate p53 at serine 15 and disrupt its interaction with MDM2.**

GLOSSARY

Enzyme: **A type of protein that speeds up a chemical reaction**

Protein: **A large molecule made of building blocks called amino acids.**

Phosphorylation: **The process of adding a phosphate group onto a molecule.**

Nucleolus: **It is found in the nucleus of the cell. It produces a type of genetic material (rRNA) and ribosomes. Ribosomes produces protein.**

PATHWAY THREE

Activated oncogenes Ras, induce the activity of the protein p14arf.

p14arf is one of two translational products of the INK4a/CDKN2A gene (p16, a cyclin kinase inhibitor, is the other product).

p14arf is regulated by E2F-1 transcription factor.

Role of p14arf

p14arf acts as a tumour suppressor where it can modify the p53–MDM2 complex by sequestering MDM2 to the nucleolus of the cell.

(Mirzayans *et al.* 2012; Sui *et al*. 2011; Liebl and Hofmann, 2021; Marei *et al.* 2021)

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HOW DOES P53 REGULATE THE TRANSCRIPTION OF ITS TARGET GENES?

1. The p53 protein binds as a tetramer to a DNA response element to regulate transcription of its target genes

2. p53 binds to approximately 300 different gene promoter regions.

GLOSSARY

Gene: Hereditary unit and short section of DNA that helps determine characteristics of an organism.

Oligomers: A molecule that has few repeating patternsthat is derived from smaller molecular unites called monomers.

Oligomerization: The process in how oligomers are formed.

Promoter: The site where transcription starts. It is also the name of the site where in conjunction with an initiator it leads to a production of cancer.

Tetramer: A oligomer that is made of four monomer units.

Transcription: The process of using DNA as a template to make the single strand of nucleotide called ribonucleic acid (RNA).

(Mirzayans *et al.* 2012; Sui *et al*. 2011; Liebl and Hofmann, 2021; Marei *et al.* 2021)

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NEW RESEARCH ON P53 THERAPY

(Peuget, Zhou and Selivanova, 2024)

p53 is a good therapeutic target because of the following reasons:

- Its **strength and potency as a tumour suppressor.**
- Many cancers **depend on p53 inactivation**.

p53-centred therapy aims to do the following:

- Repair the function of p53 as a tumour suppressor by **protecting against negative regulators: MDM2 and MDMX**.
- MDM2 inhibitors include **proteolysis-targeting chimera.**
- I**mmune-based therapies**.
- **Ongoing clinical trials before approval.**

GLOSSARY

Proteolysis - the breakdown of proteins.

Chimera - a type of organism that is distinctive due to two sets of DNA or more that are different.

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NEW RESEARCH ON COMBINATION THERAPY

(Jaber, 2024)

A study partially funded by the **National Cancer Institute discovered using mice models (xenograft) that Lonsurf (previously known as TAS-102) with talazoparib (Talzenna), helped more synergistically to slow the growth of cancer cells and was effective.**

Lonsurf damages DNA in cancer cells by causing breaks and targeting one of 4 nitrogenous bases found in the DNA molecule - thymidine.

Talazoparib prevents DNA repair by targeting a group of enzymes called PARP.

This helped minimize side effects because the Lonsurf concentration needed to kill p53 mutant cancer cells decreased.

Normal TP53 gene in mice with colorectal cancer - **they had the same effect** as either of the two drugs worked alone.
TP53 mutant gene in mice with colorectal cancer - **More effective when the two drugs are combined** increasing the quality of life.

Ongoing trial to **find optimal dose and evaluate side effects moving from mice models to patient subjects with TP53 mutant colorectal cancers.** If results are positive, th**ey will proceed with other types of cancer that have high TP53 mutant gene levels: pancreatic and breast.**

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